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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): SEQ-2001-UT2

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on (Via Fax) May 1, 2006

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Application Number	Filed
08/788,988	01/23/1997

First Named Inventor: Daniel P. Little

Art Unit	Examiner
1743	Yelena G. Gakh

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71 Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 47,609
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34

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NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 4 forms are submitted.

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Application No. 08/786,988 Docket No. SEQ-2001-UT2

Introduction

Claims 108-146 are pending. Claim 108 is directed to a process for depositing a defined amount of a 3-hydroxypicolinic acid (3-HPA) matrix at discrete locations on a substrate, resulting in a substrate having discrete spots consisting essentially of the matrix. The process includes depositing a defined and controlled 0.2 to 20 nanoliter volume of a solution comprising the matrix and a solvent. The resulting substrates are useful for matrix-assisted laser-desorption ionization (MALDI) mass spectrometric analysis. Claims 109-146 depend from claim 108.

In the final Office action dated November 30, 2005, the Office rejected claims 108-146 under 35 U.S.C. §103 for alleged obviousness in view of two combinations of documents: (1) Nicola, Li, Hayes and Hancock ("Combination 1"), and (2) Vestal, Vorm, Hayes and Hancock ("Combination 2"). The Office also rejected claims 144 and 145 for alleged indefiniteness under 35 U.S.C. §112, second paragraph.

Applicants respectfully traverse the rejections because a *prima facie* showing has not been established under 35 U.S.C. §103 or 35 U.S.C. §112, second paragraph.

The Pending Claims Are Not *Prima Facie* Obvious

Claimed matter is *prima facie* obvious only when a combination of cited documents (1) teaches or suggests all of the claimed elements, (2) the person of ordinary skill in the art was motivated to modify the document(s) as suggested in the Office action, and (3) there was a reasonable expectation of success. See MPEP 2142, et seq. Combination 1 and Combination 2 fail to meet all three criteria.

1. The Cited Combinations Fail to Teach or Suggest All of the Claimed Elements

Each of Combination 1 and Combination 2 fails to teach or suggest a process in which 0.2 to 20 nanoliter volumes of 3-HPA are deposited on a substrate. Vorm, Nicola and Li fail to teach or suggest processes that include this element. Even though Li discusses a method that reduces "the sample presentation surface with respect to the laser desorption site," Li demonstrates the method utilizing 0.9 μL of matrix (i.e., 900 nanoliters), a volume far greater than in the claims. That Li states the apparatus utilized could deliver as "little as 20 pL of sample" is of no consequence since this parameter pertains to analyte volume, which is not an element of the pending claims. Applicants also have established the size of the matrix layer deposited in Li is far larger than each spot resulting from the claimed methods (e.g., Applicants' October 14, 2005 response, pages 9 and 12). Vorm discusses methods in which 0.5 μL of matrix (i.e., 500 nanoliters) is spotted on a probe tip, and Nicola spots even greater volumes (2.5-10 μL).

Applicants established the size of the matrix spot deposited in Vorm and Nicola is larger than the spots deposited by the claimed processes (e.g., Applicants' October 14, 2005 response, pages 9 and 11-12). In addition to their failure to teach or suggest processes for depositing the volumes of matrix claimed, Vorm, Nicola and Li also fail to mention (i) the 3-HPA matrix and (ii) spotting the matrix at multiple discrete locations on a substrate.

Vestal and Hancock also fail to discuss the claimed volumes of 3-HPA lacking in Vorm, Nicola and Li. The Office acknowledges that Vestal discusses a process in which 100 nanoliter volumes containing matrix and an analyte are spotted onto a substrate, not the 0.2 to 20 nanoliter volumes of 3-HPA without an analyte, as specified by the claims. Hancock, while mentioning 3-HPA in a listing of matrix types, does not describe the volume of matrix or how matrix is applied to an ionization surface. Hancock calls for a "10,000:1 molar ratio of matrix/analyte," a comparatively large amount of matrix (column 6, lines 16 to 26). Thus, Vestal and Hancock also fail to teach or suggest the claimed volumes of 3-HPA.

Hayes does not teach or suggest processes of depositing the claimed volumes of 3-HPA because there is no mention of mass spectrometry or any matrix in the document. The Office has not established the apparatus discussed in Hayes can deliver defined and controlled 0.2 to 20 nanoliter volumes of 3-HPA, as required by the pending claims. The lack of this showing is significant as Applicants found delivering volumes of 3-HPA matrix can clog piezoelectric apparatus components, the type of components addressed in Hayes (e.g, Applicants' specification, page 26, line 8). Thus, Hayes fails to teach or suggest the claimed volumes of 3-HPA.

Accordingly, Combination 1 and Combination 2 fails to teach or suggest a process in which a 0.2 to 20 nanoliter volume of 3-HPA is deposited at multiple discrete locations on a substrate.

2. There Was No Motivation to Combine or Modify the Cited Documents

The Court of Appeals for the Federal Circuit (CAFC) in *In re Rouffet*, 47 USPQ.2d 1453 (Fed. Cir. 1998) reversed a finding of unpatentability by the Board of Appeals on the basis there was no motivation to combine the documents cited for the rejection of Rouffet's claims. The Court identified three possible bases for motivation to combine documents.

The first listed basis, "the nature of the problem to be solved," is not found here as the pending claims are directed to processes for preparing substrates useful for MALDI mass spectrometric analysis and Hayes makes no mention of mass spectrometry, or any suitable matrix or any substrate. The stated objective of Hayes is to generate substrates having an array of probes useful for diagnostics (e.g., column 2, lines 36-39 and title), not for generating mass spectrometric

substrates. The person of ordinary skill in the art therefore would not have combined or modified other documents in Combination 1 and Combination 2 with Hayes. Further, Nicola, Vorm and Li are directed to analysis of proteins (Nicola and Vorm) and cells (Li) and therefore utilize matrix solutions different than 3-HPA, the latter of which is utilized for analysis of DNA. As protein/peptide matrix solutions have different properties than 3-HPA (Thomas Becker Declaration, paragraphs 4 and 5), there was no motivation to apply Nicola and Li in Combination 1, or Vorm in Combination 2, to the pending claims.

The second basis, "the teachings of the prior art," is not found here either as there is no motivation provided by the documents themselves. In fact, certain documents teach away from the pending claims and teach away from other documents cited by the Office. In Combination 1, Nicola teaches away from Li and Hayes and the pending claims. Nicola asserted greater crystal thickness was essential for improved signal reproducibility, owing to the greater amounts and volumes of matrix over what is claimed (e.g., Applicants' October 14, 2005 response, pages 11-12). The approach in Nicola is in contrast to the procedures discussed in Li, in which "a very thin matrix layer" was described, and is in contrast to utilizing smaller volumes of matrix. Thus, the volumes discussed in Hayes are improperly applied to Nicola, especially given the Office has not established the apparatus of Hayes could deliver the claimed volumes of 3-HPA (see above). Nicola also teaches away from the smaller volumes of matrix applied in the claimed processes. There accordingly was no motivation to combine or modify Nicola with Hayes or Li in Combination 1, and there was no motivation to apply Nicola to the processes of the pending claims.

Similarly, in Combination 2 Vorm teaches away from Hayes and from the claimed processes. Vorm asserted the surface area of the matrix should be "very large," which discouraged the person of ordinary skill in the art to reduce the amount or volume of matrix applied to a substrate (e.g., Applicants' October 14, 2005 response, pages 9-10). Accordingly, the volumes discussed in Hayes were incorrectly applied to Vorm (similar to the situation with Nicola discussed above). The approach in Vorm also is in contrast to the comparatively small volumes of matrix applied in the claimed processes. Thus, the teachings of the cited documents show the person of ordinary skill in the art would not have combined or modified Nicola with Li or Hayes in Combination 1, or Vorm with Hayes Combination 2, and would not have applied or modified Nicola or Vorm with respect to the pending claims.

The third basis is "the knowledge of persons with ordinary skill in the art." In order to apply this basis, the Court stated it would be necessary to "explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have

suggested the combination" and concluded that "the Board merely invoked the high level of skill in the field of the art. If such a rote indication would suffice to supply a motivation to combine, the more sophisticated scientific discovery would rarely, if ever, experience a patentable technical advance." The CAFC further commented that the knowledge of persons of ordinary skill in the art may include certain references of special importance (i.e., that one or both of the cited documents is so well known that anyone in the art would be familiar with the documents). An example would be the famous Kholer and Millstein paper on monoclonal antibody preparations.

Here, the Office has not articulated the specific understanding or technological principal within the knowledge of one of ordinary skill in the art that would have led to combining or modifying the cited documents. The documents cited also do not rise to the level of importance that they can be deemed documents of special importance. Thus, there is no showing that it was within the level of ordinary skill in the art to combine or modify the cited documents and arrive at the claimed methods.

Accordingly, the person of ordinary skill in the art would not have modified or combined the documents cited in Combination 1 and Combination 2.

3. "Obvious to Try" Is An Improper Rationale: There Was No Reasonable Expectation for Success

The Office's modification of the cited documents is based upon an impermissible "obvious to try" rationale. The CAFC clarified it must be determined whether the prior art, and not Applicants' disclosure, suggested to one of ordinary skill in the art that the claimed process should be carried out and would have a reasonable likelihood of success. *In re Dow Chemical*, 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988).

The cited documents of Combination 1 and Combination 2 do not suggest the claimed processes should be performed. Rather, 3-HPA applied under the conditions reported in the cited documents yields a crystal morphology that does not provide consistent mass spectra results (Thomas Becker Declaration, paragraph 4). It was not until the claimed substrates were generated using the methods and equipment described in the specification and then analyzed, that it was determined they could be successfully utilized for reproducible mass spectrometric analysis (e.g., Thomas Becker Declaration, paragraph 5). Accordingly, the documents cited in Combination 1 and Combination 2 provided no reasonable expectation that substrates useful for mass spectrometric analysis could be successfully produced, and therefore, the claimed processes are not obvious.

4. Impermissible Hindsight

Applicants respectfully address the last paragraph of page 9 in the final Office action dated November 30, 2005. The Office cited a portion of the specification that shows substrates produced by the claimed methods are useful for mass spectrometric analysis, and asserted the results were not unexpected. Applicants do not understand this position. No formal arguments directed to unexpected results were recently submitted as there is considerable evidence the claimed processes are not *prima facie* obvious. Given the lack of a *prima facie* showing of obviousness based on the cited documents, Applicants are concerned the Office is impermissibly asserting obviousness based upon the teachings of Applicants' specification. It has long been held that an obviousness rejection may not be founded upon the teachings of the specification and the use of hindsight (e.g., *In re McLaughlin* 170 USPQ 209 (CCPA 1971)). Applicants respectfully conclude the rejections under Combination 1 and Combination 2 are based upon impermissible hindsight given (1) the deficiencies of the rejections described above, and (2) the Office's focus on knowledge gained and reported in Applicants' specification.

Claims 144 and 145 Are Not *Prima Facie* Indefinite

Claims 144 and 145 specify the spot sizes are "defined by" two-dimensional parameters. It is possible to define the maximum surface area of a circular spot by two-dimensional parameters. For example, a the maximum diameter of a circle can be limited by each side of a square in which the circle resides (e.g., Applicants' October 14, 2005 response, page 7). Thus, the subject matter of claims 144 and 145 are clear and are not *prima facie* indefinite.

Conclusions

Pending claims 108-146 are not *prima facie* obvious because (1) the cited documents, in combination, fail to teach or suggest a process in which 0.2 to 20 nanoliter volumes of 3-HPA matrix are deposited at discrete locations of a substrate; (2) documents cited are incorrectly combined or modified since certain documents teach away from disclosures of other cited documents and from the claimed processes; and (3) the cited documents provide no reasonable expectation for successfully generating substrates useful for mass spectrometric analysis. Accordingly, the obviousness rejections are founded upon hindsight in view of the Office's focus on the teachings of Applicants' specification. And claims 144 and 145 are not *prima facie* indefinite given the analysis above. Accordingly, Applicants respectfully request withdrawal of the outstanding rejections and issuance of a Notice of Allowance.